

Remarks

Claims 49-50, 52-53 and 56-77 are pending. Claims 52, 53, 56, 57 and 77 have been amended to remove their multiple dependency. Claims 50, 67, 68 and 69 have been amended to remove the recitation of the phrase “a blood sample which comprises leukocytes which have not been fractionated into cell types” without prejudice. Claim 70 has been amended to specify that the statistical significance has a p value < 0.05 . Claim 61 has been amended to specify that the controls are healthy controls. Claims 62, 63 and 73 are cancelled without prejudice. Claims 64 and 65, have been amended to remove the dependency on newly canceled claims. Support for these amendments are found throughout the specification and in the claims as originally filed. No new matter has been entered.

Claims Objection

Claims 52, 53, 56, 57 and 77 are objected to under 37 C.F.R. 1.75 (C) as being in improper form. Claims 52, 53, 56, 57 and 76 have been amended to remove their multiple dependency.

Claims Rejection - 35 U.S.C. 112 2nd

Claims 59, 60-65, 67, 68, 69 and 71-75 are rejected under 35 U.S.C. 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The office Action states that claim 59 depends from itself and is rejected as indefinite. Accordingly, Applicant has amended claim 59 so that it depends from claim 58.

Claims Rejection - 35 U.S.C. 112 1st written description

Claims 50, 67, 68 and 69 are rejected under 35 U.S.C. 112, 1st paragraph, as failing to comply with the written description requirement on the grounds that the instantly recited phrase “comprises leukocytes which have not been fractionated into cell types” is new matter. Although Applicant respectfully traverses, Applicant has amended the instant claims by removing the recitation of the phrase “a blood sample which comprises leukocytes which have not been fractionated into cell types” from the instant claims without prejudice.

Claims Rejection - 35 U.S.C. 112 1st enablement

Claims 49, 50, 58 and 60-76 are rejected under 35 U.S.C. 112, 1st paragraph, as failing to comply with the enablement requirement.

Applicant respectfully traverses. Applicant disagrees with the rejection's assertion that the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention in view of the breadth of the claims, the amount of guidance provided by the specification and the level of predictability in the art.

Independent claim 49 is drawn to a method for detecting rheumatoid arthritis in a human test subject comprising: quantifying a level of RNA encoded by a CDCA1 gene in a blood sample of the test subject, and comparing it with that of control subjects which are classified as healthy control subjects and with control subjects which are classified as having rheumatoid arthritis.

Independent claim 58 is drawn to a method for detecting expression of a CDCA1 gene in a human test subject comprising detecting RNA encoded by the gene in a blood sample of the test subject, using an oligonucleotide of predetermined sequence which is specific only for RNA encoded by said gene in said sample, and/or for cDNA complementary to RNA encoded by said gene in said sample.

Independent claim 66 is drawn to a method of screening a human test subject for being a candidate for having rheumatoid arthritis, said method comprising: (a) detecting RNA encoded by a CDCA1 gene in a blood sample of said test subject, (b) quantifying a level of RNA encoded by the gene in said sample of the test subject; and (c) comparing the level of RNA in the sample of the test subject to a quantified level of control RNA encoded by the gene in blood samples of control subjects classified as healthy subjects, wherein the test subject is a candidate for having rheumatoid arthritis if said level of RNA encoded by said CDCA1 gene in said blood sample of said human test subject is significantly different relative to that of said control subjects classified as healthy subjects with a p value less than 0.05.

Independent Claim 70 is drawn to a method of classifying CDCA1 gene expression in a test subject relative to a population of control subjects that includes subjects having rheumatoid arthritis and healthy subjects. Claim 70 comprises a step of quantifying a level of RNA encoded

by a CDCA1 gene in a blood sample from the test subject, and a subsequent step of comparing the level in the sample from the test subject with levels of RNA encoded by the gene in blood samples from the subjects having rheumatoid arthritis and in blood samples from the healthy subjects. The claim concludes that a statistically significant determination that the level in the sample from the test subject is similar to the levels in the samples from the subjects having rheumatoid arthritis and is different from the levels in the samples from the healthy subjects classifies the level in the sample from the test subject with the levels from the samples from the subjects having rheumatoid arthritis; and that a statistically significant determination that the level in the sample from the test subject is statistically different from the levels in the samples from the subjects having rheumatoid arthritis and is statistically similar to the levels in the samples from the healthy subjects classifies the level in the sample from the test subject with the levels in the samples from the healthy subjects.

The Office Action indicates on pages 20-21 that the claims all set forth comparing the test level to a quantified level of RNA encoded by a CDCA1 gene in blood samples from control subjects, but the specification does not provide this quantified level, which the office action contends is critical to the understanding of the relationship between CDCA1 expression and rheumatoid arthritis. The Office Action further states that the nature of the difference between the test subject and controls is not disclosed, with respect to the level and direction of the difference, and that the finding was not replicated.

Applicant submits that neither the magnitude or direction of the expression of CDCA1, i.e., the “nature of the ‘difference,’” are absolutely required to enable, i.e., teach, one of ordinary skill in the art how to make and/or use the claimed invention. Instead, what is required is at least one method for enabling the invention, which is provided in the way of identifying statistically significant differentially expressed genes at a threshold of $p < 0.05$.

Applicant respectfully submits that by disclosing that CDCA1 is differentially expressed in blood of samples from individuals with rheumatoid arthritis versus healthy control subjects, Applicant has provided those of skill in the art one method, albeit not necessarily an exclusive method, to aid in identifying a likelihood of rheumatoid arthritis (e.g., relative to a likelihood of being healthy). It will be appreciated that as long as the specification discloses *at least one method* for making and using the claimed invention that bears a reasonable correlation to the

entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. See In re Fisher, 427 F.2d 833, 839 (CCPA 1970). Failure to disclose other methods (e.g., determination of magnitude and/or direction) by which the claimed invention may be made does **not** render a claim invalid under Section 112. See Spectra-Physics, Inc. v. Coherent, Inc. 827 F.2d 1524, 1533 (Fed. Cir.), *cert. Denied*, 484 U.S. 954 (1987). Moreover, the fact that Applicant has exemplified specific genes which are differentially expressed in patients with rheumatoid arthritis versus healthy controls with a p value of less than 0.05 from thousands of genes screened and with values that are often much lower than 0.05, is the nexus of the invention, and knowledge of the direction or magnitude of the differential expression is not required to practice the claims.

Indeed, methods and protocols for applying differentially expressed genes to indicate the presence of a disease or condition, ***regardless of direction of change of expression***, are well established in the art and disclosed and incorporated by reference in the specification. For example, Slonim DK, Nature Genetics Supplement, Vol. 32, 502-8 (2002), which is incorporated by reference in the instant specification at paragraph 133 of the published application (2004/0265869), states that “[t]he most basic question one can ask in a transcriptional profiling experiment is which genes’ expression levels changed significantly.” Applicant respectfully submits that Table 3M, in fact, provides which genes’ expression levels—including CDCA1 (p value of 0.035)—changed significantly; and thus, the specification comports with the methods and protocols generally accepted in the art. Submitted herewith is a copy of Slonim, which the Office is kindly asked to make of record.

The Applicant respectfully submits that the invention is taught by the specification and claimed in such terms that one skilled in the art can make and use the claimed invention, including the use of the elected biomarker, CDCA1, as classifier of rheumatoid arthritis in a tested subject (e.g., relative to being classified as healthy) without the *a priori* need to know the direction or the level of differential expression that exists between subjects having rheumatoid arthritis and healthy subjects.

Lack of directionality and/or magnitude in the specification as-filed does not render the claims of the present scope non-enabled. The Applicant has identified the elected gene CDCA1 as being differentially expressed between individuals diagnosed as having rheumatoid arthritis and healthy controls by demonstrating a statistically significant difference in the level of RNA,

as described in Example 22. The statistical significance of CDCA1's differential expression is evidenced by its p value of 0.035 as listed in Table 3M. The dendrogram of Figure 20 demonstrates that the CDCA1 gene is one of a number of genes which demonstrate a statistically significant difference between individuals who have rheumatoid arthritis and healthy individuals. Therefore, the Applicant has taught that there is a significant difference in differential expression for CDCA1 between a population of individuals having rheumatoid arthritis and a population of healthy individuals, and further has taught a method to compare the level of expression of CDCA1 in a test individual with populations having rheumatoid arthritis and populations of healthy subjects using methods to determine the similarity or difference in gene expression levels between the test subject and the tested control populations.

Support for reciting comparison of biomarker RNA levels of a test subject with those of control subjects having a disease (i.e. rheumatoid arthritis) and with those of healthy control subjects, and determination of a statistically significant difference or similarity therebetween can be found in the published application (US 20050042630), for example at paragraph [0126] (*"When comparing two or more samples for differences, results are reported as statistically significant when there is only a small probability that similar results would have been observed if the tested hypothesis (i.e., the genes are not expressed at different levels) were true"*), and at paragraph [0127] (*"When comparing two or more samples for similarities, results are reported as statistically significant when there is only a small probability that similar results would have been observed if the tested hypothesis (i.e., the genes are not expressed at different levels) were true"*), respectively. Support for reciting classification of a test subject level relative to spc control levels can be found, for example, at claim 12 as originally filed (*"d) determining whether the level of said one or more gene transcripts of step a) classify with the levels of said transcripts in step b) as compared with the levels of said transcripts in step c)"*), at paragraph [0134] (relating to *"Methods that can be used for class prediction analysis"*), paragraph [0374] (*"Blood samples were taken from patients who were diagnosed with rheumatoid arthritis as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease."*).

And, as particularly emphasized above, magnitude and/or directionality are not necessarily the key and/or exclusive determination that is needed to be made. Instead, ***[t]he***

most basic question one can ask in a transcriptional profiling experiment is which genes' expression levels changed significantly." (Slonim DK, see above). Magnitude and/or directionality are inherent features of the expression level of a gene which has been determined with statistical significance to be differentially expressed in diseased subjects versus healthy subjects. Accordingly, the Applicant believes that the specification establishes that there exists the requisite reliable association between CDCA1 expression levels in subjects having rheumatoid arthritis and healthy controls.

The office action states that it is clear that the applicant intends to use classification methods in order to provide a tool that is used as part of a diagnostic process, and such a use requires the knowledge of a reliable association underlying the classification.

The specification explicitly teaches the use of classification methods in at least paragraphs 0133-0135 and paragraph 0377 of the published instant application. In particular, paragraph 0134 describes methods that can be used for class prediction analysis, and paragraph 0377 describes that blood samples were taken from patients who were diagnosed with rheumatoid arthritis as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease.

Further, paragraphs 0133-0135 of the published application state as follows:

[0133] As would be understood to a person skilled in the art, one can utilize sets of genes which have been identified as statistically significant as described above in order to characterize an unknown sample as having said disease or not having said disease. This is commonly termed "class prediction".

[0134] Methods that can be used for class prediction analysis have been well described and generally involve a training phase using samples with known classification and a testing phase from which the algorithm generalizes from the training data so as to predict classification of unknown samples (see for Example Slonim, D. (2002), Nature Genetics Supp., Vol.32 502-8, Raychaudhuri et al., (2001) Trends Biotechnol., 19: 189-193; Khan et al. (2001) Nature Med., 7 673-9.; Golub et al. (1999) Science 286: 531-7. Hastie et al., (2000) Genome Biol., 1(2) Research 0003.1-0003.21, all of which are incorporated herein by reference in their entirety).

[0135] As additional samples are obtained, for example during clinical trials, their expression profiles can be determined and correlated with the relevant subject data in the database and likewise be recorded in said database. Algorithms as described above can be used to query additional samples against the existing database to further refine the diagnostic and/or prognostic determination by allowing an even greater association between the disease and gene expression signature".

Thus, classification methods are a well known tool used in the art to refine algorithms to more accurately diagnose disease based on identified biomarkers. Paragraph 0377 of the instant specification further discloses the use of classification of a test sample of an individual to classify said individual as having or not having rheumatoid arthritis can be done using the differentially expressed genes listed in Table 3M, which includes CDCA1. In light of the disclosed use for Claim 70, drawn to a method of classifying expression of a gene encoding CDCA1 in a human test subject, Applicant contends claim 70 is fully enabled.

The comparison step of claim 70 is between a test subject and both healthy controls and controls with rheumatoid arthritis. It does not compare other diseases. The use of the classification method is not disclosed to be an unequivocal diagnosis, but only one method in a battery of diagnostic assays to contribute to a diagnosis of rheumatoid arthritis. Further, Claim 70 is not necessarily drawn to a method of distinguishing rheumatoid arthritis from another autoimmune disease, as suggested in the office action on page 9, or another disease as suggested on page 6. In contrast, claim 70 is drawn to a classification method, which, as suggested in the office action when read in light of the specification, is designed to be used “to provide a tool that is used as part of a diagnostic process”. As such, Claim 70 contains no resolution step of diagnosing rheumatoid arthritis, and leaves open the use of other methods to confirm the diagnosis and/or the extent with which CDCA1 is useful as a marker for rheumatoid arthritis.

Regarding the concern of the office action that it is unknown and unpredictable whether CDCA1 could be expressed in the blood of patients having another disease, (e.g., SLE, as suggested on page 9 of office action), Applicant notes that even the much litigated patented method claims of Metabolite Laboratories, Inc.’s U.S. Patent No. 4,940,658, (‘658), include method steps which can be used to indicate a disease or disorder other than the disease/disorder recited. For example, Claim 13 of ‘658 is drawn to a method for detecting a deficiency of cobalamin or folate in warm-blooded animals by assaying a body fluid for an elevated level of total homocysteine, and is thus used as a method to detect vitamin deficiency. However, it was well known in the medical community before the filing of ‘658, that the assay for elevated homocysteine levels could signal an increased risk of heart disease. Despite much scrutiny for other reasons, claim 13 of ‘658 has not been invalidated as a result of other previously known use(s) of its claimed assay to provide a correlation to a second disease or disorder not recited in its claim 13.

The claims do not claim, seek, or even require the absolute diagnosis or classification of rheumatoid arthritis. The use of a biomarker, as is used in the present claims, as a type of indicator of a disease is typically just one aspect, and typically an early aspect, of a multifactorial process used in diagnosing a person as having a particular disease of interest and can be useful in providing guidance in medical decisions regarding additional testing and treatment of a disease. The claimed methods are clearly not aimed at providing a definitive diagnosis of rheumatoid arthritis, but rather a useful approach aimed to provide assistance in the early stages of evaluating a patient for rheumatoid arthritis, e.g., from a simple blood draw.

The office action indicates that the specification teaches that CDCA1 is differentially expressed in patients having lupus versus healthy controls, but that there is no means or guidance as to how to differentiate between RA and SLE or other diseases which were not tested.

The office action asserts on pages 10- 11 that neither the claims nor the specification set forth a threshold of difference between an individual's expression and the control's expression of CDCA1 in blood that would be sufficient to conclude that the difference is "indicative" of rheumatoid arthritis. As noted in Stedman's 27th Edition Medical Dictionary, indication is not equated with diagnosis. The term indication is understood to mean "the basis for initiation of a treatment for a disease or of a diagnostic test" (see page 892). Even a diagnostic test is not considered to result in an absolute certainty of a diagnosis of disease – but rather is noted as "relating to or aiding in diagnosis". As noted in Harrison's Principles of Internal Medicine, Introduction to Clinical Medicine "the purpose of performing a test on a patient is to reduce uncertainty about the patient's diagnosis or prognosis and to aid the clinician in making management decisions" (Ch I, pg. 11). This same text further notes that while "a perfect test would have a sensitivity of 100% and a specificity of 100% and would completely separate patients with disease from those without it...there are no perfect tests, after every test is completed the true disease state of the patient remains uncertain" (Ch I, pg. 11). Accordingly, in view of the above, Applicant respectfully requests that the Examiner reconsider the nature and scope of the subject matter that is actually presently claimed. It is respectfully asserted, given that the nature and scope of the invention is directed to identifying a human test subject as being a candidate for having rheumatoid arthritis (RA), classifying a human test subject as being more likely than not to have rheumatoid arthritis (e.g., classifying a human test subject as being more likely to have rheumatoid arthritis than to be healthy), or detecting expression of a CDCA1 gene

in a human test subject, one of ordinary skill in the art would not have required undue experimentation to make and/or use the present invention.

The office action indicates that some claims recite controls that do not have rheumatoid arthritis. In the interest of advancing prosecution, Applicant has amended claim 61 to specify that these controls are healthy controls and cancelled claims 62, 63 and 73, without prejudice, and changed the dependency of claims 64 and 65 to newly amended claim 61. All pending claims that require comparison with a negative control now specify that the control is healthy.

The office action states on page 7, that there is no universally accepted level of statistical significance. Accordingly, Applicant has amended claim 70 to specify that the required statistical significance have a p value of less than 0.05.

The Office Action also suggests that field of analyzing expression profiles remains highly unpredictable years after the filing of the instant application, (page 10 of the Office Action) citing Osman et al. The Applicant submits that the differential expression of CDCA1 as between subjects having rheumatoid arthritis and subjects not having rheumatoid arthritis is, in fact, predictable. In Osman et al., blood cell gene expression profiles of bladder cancer patients (i.e., 16 individuals having bladder cancer) were compared with 10 healthy individuals. A selection of the genes identified as demonstrating statistically significant difference ($p < 0.05$; page 3376) were tested using RT-PCR on yet an additional sample set of 20 bladder cancer patients and 14 control patients (page 3376, second column) and IGFBP7 continued to verify as a gene which was differentially expressed as between the two populations (see page 3377, second column).

As stated in the Manual of Patent Examining Procedure at 2164.03: the “predictability or lack thereof” in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. In the instant application, the disclosed result is a statistically significant differential expression in the level of CDCA1 RNA as between subjects having rheumatoid arthritis and subjects not having rheumatoid arthritis, the statistically significant difference having a p value < 0.05 , as indicated in Table 3M of the instant specification.

The Office Action states on pages 8-9 that Lee teaches that data obtained from gene chips must be replicated in order to screen out false positive results; on page 11, that Cheung et al. (2003) teaches that there is natural variation in gene expression amongst different individuals; on

pages 11-12 that Wu et al (2001) teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, and that the conclusions that can be drawn from a given set of data depend on the particular choice of data analysis; and on page 12 that Newton et al. (2001) teaches that a replication of data is required for validation.

Applicant respectfully disagrees with the contention based on Wu et al. that expression data needs to be interpreted in view of other biological knowledge. Differential gene expression which is reproducible, and is correlated with the state of health or disease of the individual may not necessarily result directly from the state of disease of the individual. Rather these changes in expression may simply represent a downstream side-effect of pathogenic processes, and it is not necessary that the biological relevance of the data be known to allow this difference in expression to be useful as a biomarker. For example prostate-specific phosphatase and prostate-specific antigen (PSA) were long used as biomarkers without an understanding of their function, as evidenced by Chu TM, 1990, Prostate cancer-associated markers. *Immunol. Ser.* 53:339-56; and Diamandis EP., 2000, Prostate-specific antigen: a cancer fighter and a valuable messenger? *Clin Chem.* 46:896-900), of record.

The Examiner also argues, on the basis of post-filing art of Wu (2001) and Newton (2001), that many factors may influence the outcome of the data analysis and notes that conclusions depend on the methods of data analysis. While considerations such as variability, and normalization are of importance, these considerations are well understood by a person skilled in the art and have been applied for many years to permit development of biomarkers which are indicative of disease. These challenges are well understood, as are the routine experiments required to exemplify statistically significant differences in populations.

Applicant notes that the results disclosed by Cheung *et al.* cannot be reliably extrapolated to primary blood samples since the lymphoblastoid cells employed by Cheung *et al.* are significantly modified relative to primary blood cells, due to being cultured cell lines generated by immortalization of primary human cells derived from "CEPH" families, as indicated in Reference no. 10 of Cheung *et al.* (Dausset *et al.*, 1990. *Genomics* 6:575; enclosed) at p. 575, right column, 1st paragraph. Applicant notes that immortalized cultured cell lines such as the lymphoblastoid cells taught by Cheung *et al.* undergo significant genetic modification such as strong genome-wide demethylation (refer, for example, to Vilain *et al.*, 2003. DNA methylation and chromosome instability in lymphoblastoid cell lines. *Cytogenet Cell Genet.* 90:93) of record,

as a result of extensive *in-vitro* culturing in the absence of immune or apoptotic mechanisms which function to eliminate mutated cells in the body. As such, immortalized CEPH lymphoblastoid cells may represent a particularly unsuitable cell type for modeling gene expression variability in primary blood cells.

The office action, in response to Applicant's assertion that the results of Cheung et al. can not be reasonably extrapolated to primary blood samples since Cheung et al. use cultured cell lines, contends that this is "irrelevant to the Cheung et al. which is that among individuals (in this case cell lines) there is a natural variability in gene expression for any particular gene". Applicant emphasizes that the term "individual" refers to primary blood samples composed of a highly heterogeneous mixture of cell types, not to clonal cultured cell lines, and request support from the Examiner demonstrating that the variability among cultured cell lines is analogous to the variability of blood samples from individuals in general and in particular for the gene CDCA1.

To the extent that Cheung et al. could still be considered to suggest that larger populations of diseased and control populations may be useful to determine what level of differential expression is indicative of disease amongst the population at large, the Applicant submits that the extension of the experiments as outlined in the specification to additional individuals is merely routine. As is noted in *Re Wands* "*even a considerable amount of experimentation is permissible to practice the claimed methods, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.*" (*Re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

As such the Applicant believes there is sufficient guidance provided by the specification that the CDCA1 gene is differentially expressed between human individuals who are healthy as compared to those having rheumatoid arthritis, and that the art is sufficiently predictable such that the amount of experimentation to perform the instantly claimed methods is not undue. In light of the amendments and above remarks, the Applicant contends that the claims are fully enabled, and respectfully requests reconsideration and withdrawal of the instant rejections.

Claim Rejections - 35 USC § 102

Claims 58, 60, 61, 62, 63, 67, 68, 69, 71, 72, 73 and 75 are rejected under 35 U.S.C. 102(a) and (b) as being unpatentable over Chittenden (2002).

Applicant respectfully traverses on the grounds that Chittenden does not teach every limitation of the claims. Specifically, the office action contends that it is an inherent property of the array HG-U133A that it contains probes to CDCA1. However, the office action provides no evidence that CDCA1 was actually detected by Chittenden, and further admits that Chittenden does not specifically discuss CDCA1 expression.

The office action asserts that CDCA1 would have inherently been detected in the blood of healthy controls by the hybridization and array reading methods. Applicant notes that this is an unverified assumption by the office action, and makes the assumption that there was no technical difficulties with the hybridization of nucleic acid derived from the blood sample to the CDCA1 probe on the array. Without a specific teaching that CDCA1 was detected in human blood, Chittenden does not anticipate the instant claims.

Reconsideration and withdrawal of the instant rejections is respectfully requested.

Claim Rejections - 35 USC § 103

Claims 58, 60, 61, 62, 63, 65, 67, 68, 69, 70, 71, 72, 73 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maas et al. in view of Affymetrix GeneChip Human Genome U133 Set data sheet.

Applicant respectfully traverse on the grounds that the combination of references does not arrive at the claimed invention. Specifically, the office action contends that because Maas et al looked at expression of a defined set of genes in the blood of rheumatoid arthritis patients and healthy control patients, that it would have been obvious for one of skill on the art to have to substituted a second set of genes (Affymetrix GeneChip Human Genome U133) using the techniques of Maas et al. Neither Maas et al. nor the Affymetrix data sheet teach any relationship between CDCA1 and rheumatoid arthritis. Thus the cited references would only be combined by one of skill having the benefit of Applicant's specification, and as such is hindsight. Accordingly, Applicant respectfully traverse the rejection, and request reconsideration and its withdrawal.

Claim Rejections - 35 USC § 103

Claims 58, 59, 60, 61, 62, 63, 65, 67, 68, 69, 70, 71, 72, 73 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heller et al., in view of Affymetrix GeneChip Human Genome U133 Set data sheet and Sharma et al.

Applicant respectfully traverse on the grounds that the combination of references does not arrive at the claimed invention. Specifically, the office action contends that because Heller et al looked at expression of a defined set of genes in the blood of rheumatoid arthritis patients and healthy control patients, that it would have been obvious for one of skill on the art to have to substituted a second set of genes (Affymetrix GeneChip Human Genome U133) using the techniques of Heller et al. Neither Heller et al. nor the Affymetrix data sheet teach any relationship between CDCA1 and rheumatoid arthritis. Thus the cited references would only be combined by one of skill having the benefit of Applicant's specification, and as such is hindsight.

The office action admits that Heller et al does not teach the use of an array which includes CDCA1, and further contends that one of skill would have been motivated to modify the methods of Heller et al. to incorporate the Affymetrix gene chip, by Sharma et al.'s teachings that disease exerts a global effect on individuals and that this effect can be measured by gene expression in blood.

Applicant submits that the generic teaching by Sharma is not sufficient motivation to apply the teachings of Heller et al. to detect expression of a CDCA1 gene in blood of a human test subject having rheumatoid arthritis because it provides no substantive scientific basis to predictably arrive at the claimed invention of identifying a CDCA1 gene as a candidate marker for rheumatoid arthritis based on its specification.

The Office Action indicates that Sharma et al teaches: "From the very early stages of diseases caused by infections, toxic substances, ageing or other conditions changing the quality of life of living eukaryotic organisms, the whole organism responds to the changed condition", page 10, 4th full paragraph, WO 98/49342

and

"The invention is a quick and precise method for the diagnosis of *any disease or condition that leads to alterations in the activity of genes* in a pattern which is specific to any particular condition of the organism under observation", emphasis added, page 10, 2nd full paragraph, WO 98/49342.

The latter paragraph indicates that Sharma's teachings do not necessarily apply to every disease, but only to those disease(s) that "leads to alterations in the activity of genes in a pattern which is specific to any particular condition of the organism under observation". Further, Sharma et al. provides not a single piece of preliminary data of differential expression in whole blood of any RNA with respect to disease, including rheumatoid arthritis.

Accordingly, Applicant contends that the neither the prophetic nor the non-prophetic working examples of Sharma et al. provide sufficient motivation for one of skill reading Sharma's WO document to modify the methods of Heller et al. by substituting whole blood as the source to identify and use CDCA1 to detect/classify rheumatoid arthritis.

Applicant respectfully traverses, on the grounds that one guideline published by the USPTO for determining obviousness after KSR (Federal Register, Vol. 72, No. 195; October 10, 2007) is that a simple substitution of one known element for another to obtain predictable results. As discussed above, Sharma et al.'s prophetic examples do not provide a reliable scientific basis for practicing the claimed methods of identifying biomarkers useful in detecting rheumatoid arthritis in blood with a reasonable expectation of success. Thus, it would not have been predictable based on the cited art to one of skill in the art at the time the invention was made, who was considering combining the methods of Heller et al. with Sharma et al. by using the Affymetrix gene chip array to identify CDCA1 as a candidate biomarker for rheumatoid arthritis, that such a combined method would be successful and/or predictably arrive at the claimed invention. In the absence of predictability in arriving at the claimed invention by substituting the genes looked at by Heller et al. with those on the Affymetrix chip, one of skill would not have had a reasonable expectation of success in practicing the claimed invention, and thus no prima facie case of obviousness can be made.

In light of the amendments and above remarks, the Applicant contends that the claims are fully enabled, and respectfully requests reconsideration and withdrawal of the instant rejections.

Conclusion

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. No new matter is added. If the Examiner believes that a

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telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

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